IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Raymond P. WARRELL et al.

Application No.: 09/709,170

Filed: November 10, 2000

For: METHODS OF TREAMENT OF A BCL-2 DISORDER USING BCL-2 ANTISENSE OLIGOMERS

Art Unit: 1635

Examiner: Terra C. Gibbs

Confirmation No.: 4982

Atty. Docket No.: GEN0008-01US

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed on June 20, 2008, for the subject application, a brief in support of the appeal is now submitted. Submission of a brief in support of the appeal in this case was due by August 20, 2008. Accordingly, a petition to extend the time for filing the brief by one month is being submitted herewith.

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REAL PARTY IN INTEREST

The real party in interest is Genta Incorporated, the assignee of record.

RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences that are related to this appeal, or which will affect or have a bearing on this appeal.

STATUS OF CLAIMS

Claims 1, 3-5 and 7-23 were finally rejected in an Office Action mailed on March 25, 2008 ("the Final Office Action"), and are the subject of this appeal. Claims 2, 6 and 24-33 were previously cancelled without prejudice or disclaimer.

STATUS OF AMENDMENTS

No claims have been amended, cancelled or added subsequent to the Final Office Action.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter encompasses a method of treating cancer in a human comprising administration of a bcl-2 antisense oligonucleotide. Independent claim 1 is directed to a method of treating cancer in a human comprising:

> administering to said human, in which such treatment is desired, a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily *(page 5, lines 18-20; page 13, line 24 to page 14, line 9)*,
>
> in more than one cycle of therapy *(page 7, lines 28-35)*,
>
> each cycle of therapy consisting of 3-9 days *(page 5, lines 15-17; page 16, line 13-14)*,
>
> wherein each cycle of therapy is separated by an interval of time wherein said human receives no bcl-2 antisense oligonucleotide *(page 7, lines 28-35; page 31, lines 4-9; page 39, lines 19-21)*, and
>
> wherein said interval of comprises at least one day *(page 7, lines 28-35; page 31, lines 4-9; page 39, lines 19-21)*, and
>
> further comprising administering one or more cancer therapeutics *(page 4, line 35 to page 5, line 3; page 17, lines 30-31; page 31, lines 7-9; page 39, lines 8-10; page 41, lines 6-7)*.

Independent claim 19 is directed to a method of treating cancer in a human, comprising:

> administering to said human, in which such treatment is desired, one or more chemoagents and a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily *(page 4, line 35 to page 5, line 3; page 5, lines 18-20; page 13, line 24 to page 14, line 9; page 17,*

lines 30-31; page 31, lines 7-9; page 39, lines 8-10; page 41, lines 6-7),

in more than one cycle of therapy *(page 7, lines 28-35)*,

each cycle of therapy consisting of 3-9 days (page 5, lines 15-17; page 16, line 13-14),

wherein each cycle of therapy is separated by an interval of time wherein said human receives no bcl-2 antisense oligonucleotide *(page 7, lines 28-35; page 31, lines 4-9; page 39, lines 19-21), and wherein said interval of comprises at least one day (page 7, lines 28-35; page 31, lines 4-9; page 39, lines 19-21)*, and

wherein the chemoagent is dacarbazine, docetaxal, paclitaxal, cisplatin, 5-flurouracil, doxorubicin, etoposide, cyclophosphamide, fludarabine, irinotecan or cytosine arabinoside (Ara-C) *(page 18, line 25 to page 19, line 19)*,

administered at a dose which is below the effective dose when the chemoagent is administered without the bcl-2 oligonucleotide *(page 20, lines 6-9)*.

The dependent claims are directed to various embodiments of the disclosed method. In particular, claim 5 is directed to the method of treating cancer in a human of claim 1 or 3, comprising administering 5 to 7 mg/kg/day of the bcl-2 antisense oligonucleotide *(page 5, lines 18-20; page 16, lines 10-17; page 31, lines 15-18; page 39, lines 8-10)*.

A copy of the appealed claims is appended hereto, beginning at page 25.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Whether claims 1, 3-5 and 7-23 are unpatentable under 35 U.S.C. § 103(a) as obvious over Webb et al. (*Lancet* 349:1137-1141 (1997); "Webb") in view of Waters et al. (*J. Clin. Oncol.* 18:1812-1823 (2000); "Waters") and Bennett et al. (U.S. Pat. No. 6,214,986; "Bennett").

ARGUMENT

SUMMARY OF THE ARGUMENT

Appellants respectfully set forth this appeal brief on two primary grounds, among other grounds. First, none of the cited art provides the claim elements of "more than one cycle of therapy," "3 to 9 days," and "separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered." It is only through the impermissible use of hindsight that the Examiner arrives at a conclusion that the cited art could be modified so as to arrive at such a cycle of therapy of 3 to 9 days. Moreover, this conclusion was made by the Examiner in direct disregard of the evidence of record, namely the declaration of Dr. Steven Craig Novick. Second, the Examiner's use of inherency to render the claims obvious is misplaced and contrary to case law because the cited art fails to provide the ***same*** steps as the pending claims.

I. Rejection Under § 103(a) Over Webb in View of Waters and Bennett

Claims 1, 3-5 and 7-23 stand finally rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Webb in view of Waters and Bennett. The Examiner rejected the claims in the Final Office Action for the reasons of record set forth in the Office Action mailed on August 22, 2007. According to the Examiner in that Office Action, Webb teaches bcl-2 antisense therapy at a dose of 4.6 mg/m^2 to 73.6 mg/m^2 in human patients with non-Hodgkin lymphoma. Specifically, Webb is said to disclose the reduction of bcl-2 protein levels in lymph node aspirates of Patient 6 after a 7-day course of therapy using a fully phosphorothioated bcl-2 antisense oligonucleotide ("ASO"), which is 100% identical to SEQ ID NO: 17 of the instant application. The Examiner acknowledges that Webb is silent regarding whether cancer was treated in Patient 6 at 7 days, but asserts that since the instant claims are drawn to a method of treating cancer in a human comprising one step, namely the administration of a bcl-2 ASO for 3-

9 days, the cancer in patient 6 was inherently treated. Citing § MPEP 2112, the Examiner would shift the burden to Appellants to show that the teachings of Webb would not treat cancer at day 7 under generally any assay condition.

Also acknowledging that Webb does not teach more than one cycle of therapy separated by an interval of time of at least one day wherein no bcl-2 ASO is administered, and wherein the therapy includes administration of one or more cancer therapeutics, the Examiner asserts that Waters teaches interrupted bcl-2 ASO therapy in human patients with non-Hodgkin lymphoma. According to the Examiner, a second course of treatment was administered to Patients 2, 17 and 21. In particular, Patient 17 was retreated 48 hours after his initial course of therapy. Regarding the administration of one or more cancer therapeutics, the Examiner states that Bennett teaches the administration of bcl ASOs with one or more cancer agents that function by a non-antisense mechanism, such as 5-FU, etoposide and cisplatin. Bennett is also said to teach that "Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates."

Thus according to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to devise the claimed method of treatment using the teachings of Webb and Waters. One would have been motivated, per the Examiner, to devise the method since Webb taught the reduction of bcl-2 levels in Patient 6 after 7 days of treatment and Waters teaches interrupted ASO therapy. The Examiner further purports that one also would have been motivated to add cancer therapeutics since Bennett teaches it is routine to add such agents to ASO treatment. One of ordinary skill in the art, according to the Examiner, would have expected success at devising the claimed method since Webb teaches the successful use of bcl-2 ASO therapy in a human for 3-9 days and Waters teaches interrupted ASO therapy.

Appellants submit that the Examiner's conclusion regarding the obviousness of the claimed invention constitutes error and must be reversed.

In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. *See In re Fine*, 837 F.2d 1071, 1073, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In so doing, the Examiner must make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), *viz.*, (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; and (3) the level of ordinary skill in the art. "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Furthermore, although the analysis need not identify explicit teachings directed to the claimed subject matter, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1396 (2007). As such, "'there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

Claims 1 and 19 (and thus claims 3-5 and 7-18 and 20-23 dependent therefrom) are directed to a method of treating cancer in a human comprising, *inter alia*, administering a bcl-2 ASO in ***more than one cycle of therapy***, each cycle of therapy consisting of ***3 to 9 days***, wherein each cycle of therapy is ***separated by an interval of time wherein no bcl-2 antisense***

oligonucleotide is administered. The invention is based, in part, on the discovery that short treatment cycles and/or high doses of bcl-2 ASO, alone or in combination with other therapeutic agents, unexpectedly provides greater ameliorative effects with less toxicity in human patients suffering from cancer compared to previous treatment regimens. *See* page 9, line 20 to page 10, line 4. Appellants maintain that Webb in view of Waters and Bennett does not suggest to one skilled in the art such a method of treating cancer in a human because the elements of "more than one cycle of therapy," "3 to 9 days," and "separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered" are missing from the cited art. Moreover, the alleged motivation to modify the cited art provided by the Examiner is a result of impermissible hindsight.

A. Webb

Webb discloses the administration of a bcl-2 ASO to patients with non-Hodgkin lymphoma over a 2-week treatment course. *See* page 1138. Webb is relied upon by the Examiner as disclosing administration of a bcl-2 ASO for the treatment of cancer, wherein a single patient (patient 6) had reduced bcl-2 levels at day 7, a near partial response in tumor shrinkage at day 14, and reduced number of circulating lymphoma cells at day 14. The Examiner acknowledges that Webb is silent regarding whether cancer was treated in patient 6 at day 7, but asserts that since the instant claims and Webb are directed to the same step, namely the 7-day administration of a bcl-2 ASO to a cancer patient, the cancer in patient 6 was inherently treated. This, according to the Examiner, is enough to shift the burden to the Appellants under MPEP § 2112 to prove that the teachings of Webb would not have the additional benefit of treating cancer at day 7.

Here, Appellants submit that the principle of inherency has no place in this case. For a claimed method to be inherent in a prior art method, and therefore one which merely identifies a new, advantageous property of the prior art method, the methods must have the ***same*** steps. *See Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809-10 (Fed. Cir. 2002). Although the Examiner asserts that Webb teach the only method step recited in the instant claims, this is clearly not the case. Webb discloses administration of bcl-2 ASO for ***14 days***, whereas the claims recite administration of bcl-2 ASO for ***3-9 days***. In no way can it be said the two methods comprise the same steps. One need only contrast the instant case with the decision in *Bristol-Myers Squibb v. Ben Venue Labs.*, 246 F.3d 1368 (Fed. Cir. 2001), where inherency was appropriately applied, to note the striking difference.

In *Bristol-Myers*, claim 1 of the patent at issue read, "A method for reducing hematologic toxicity in a cancer patient undergoing taxol treatment comprising parenterally administering to said patient an antineoplastically effective amount of about 135-175 mg/m^2 taxol over a period of about three hours." *See id.* at 1371. An article by Kris was asserted as anticipating claim 1 in which Kris treated patients with three-hour infusions of paclitaxel within the claimed dosage ranges but observed no antitumor response. *See id.* at 1372. The Federal Circuit held that notwithstanding the lack of antitumor response, Kris anticipated claim 1 because "the claimed process here is not directed to a new use; it is the same use, and it consists of the ***same steps*** as described by Kris. Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Id.* at 1376 (emphasis added); *see also Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1369 (Fed. Cir. 2006) ("All of the steps of the '176 patent are thus disclosed in the '211 patent in furtherance of the same purpose:

the delivery of safe, effective sevoflurane anesthetic. All that is contributed by the method of the '176 patent is the recognition of a new property of the prior art process.").

Inherency, as advanced by the *Bristol-Myers* court, would perhaps be relevant to this case if, for instance, the instant claims were directed to a method for effecting tumor regression comprising administration of bcl-2 ASO for 14 days, and Webb did not identify this effect. In such a case, the identification of tumor regression could be said to be a "newly discovered result of a known process." But the instant claims are ***not*** so directed. The instant claims recite administration of bcl-2 ASO for ***3-9 days***. In sharp distinction, Webb discloses administration of bcl-2 ASO for ***14 days***. Concluding that the discovery that administration of 0.01 to 50 mg/kg daily of bcl-2 ASO for 3-9 days is efficacious for treating cancer is merely a "new property" of the prior art 14-day method is not only contrary to case law, but would mean that no novel shortened dosage regimen would ever be patentable. Moreover, it is improper for the Examiner to conclude that "subject matter cannot be patented on the basis of an inherent property," as noted in *In re Adams*:

> Finally, the solicitor adds the argument that the superiority of appellant's heat transfer is inherent in the use of foam. Again we observe that, of course, it is. But the art does not suggest the use of foam in heat transfer of any kind and there is not the slightest suggestion that anyone knew of the existence of this inherent superiority until Adams disclosed it. After all, Bell's telephone was "inherently" capable of transmitting speech, DeForest's triode was "inherently" capable of amplification, and, to come down to date, so was the tiny transistor which is rapidly supplanting it. Two of our decisions are cited as supporting the erroneous notion that "subject matter cannot be patented on the basis of an inherent property." We think the proposition thus broadly stated and as applied here is so transparently erroneous as not to require discussion.

356 F.2d 998, 1003 (CCPA 1966); *see also Eli Lilly and Co. v. Barr Labs.*, 251 F.3d 955, 976 (Fed. Cir. 2001) (Newman, J., dissenting) ("[E]very biological property is a natural and inherent

result of the chemical structure from which it arises, whether or not it has been discovered. To negate the patentability of a discovery of biological activity because it is "the natural result" of the chemical compound can have powerful consequences for the patentability of biological inventions.").

Perhaps sensing the impropriety of the inherency argument, the Examiner also relies on the standard "motivation" rubric under § 103. According to the Examiner, because patient 6 exhibited evidence of tumor shrinkage and had a decrease in the number of circulating lymphoma cells, one skilled in the art would have been motivated to shorten the course of treatment to 7 days to determine whether the favorable results would have been seen at the shortened time point. It is only through the impermissible use of hindsight that the Examiner could draw such a conclusion. *See* M.P.E.P. § 2142

The Examiner appears to be suggesting that any time a dosage regimen is disclosed in the prior art, one skilled in the art would naturally seek to identify the shortest time point within the regimen which provides a favorable response. Again, this would mean that no novel shortened dosage regimen would ever be patentable, which surely is not the case. Furthermore, such an assertion is contrary to the evidence of record. According to the Declaration of Dr. Steven Craig Novick Under 37 C.F.R. § 1.132, submitted on July 16, 2007 ("Novick Decl."; appended hereto), although Webb does disclose that patient 6 had reduced bcl-2 levels at day 7 of treatment, this fact does not provide evidence of treatment or response, nor motivation to shorten the regimen. *See* Novick Decl., page 3, ¶ 12. One skilled in the art would not know whether the total infusion of 14 days was necessary to provide a treatment of cancer, particularly since patient 6 did not show a promising cancer response. *See id.* According to Dr. Novick, one skilled in the art reading Webb would not be motivated to shorten the course of therapy simply because one

patient showed reduced bcl-2 levels at weeks 1 and 2, but rather would be motivated to continue with the longer course of therapy. *See id.*, ¶ 13.

Appellants submit that it was error for the Examiner to disregard Dr. Novick's conclusions, instead substituting her own opinion that patient 6 in Webb represented a successful treatment. Tab A to Dr. Novick's declaration provides examples of the prior art showing that the generally accepted course of bcl-2 ASO therapy was a 14-day treatment regimen. *See id.*, page 1, ¶ 3. It was not until ***after*** Appellants' invention that others moved to shorter cycles of therapy. *See id.*, ¶ 4 and Tab B. This provides irrefutable evidence as to the deficiencies of Webb and the nonobviousness of the claimed method of treatment.

B. Waters

Waters discusses additional results of the Webb study and, thus, like Webb, discloses the administration of a bcl-2 ASO to patients with non-Hodgkin lymphoma over a ***14-day*** treatment course. *See* page 1813. Waters is relied upon by the Examiner as disclosing interrupted bcl-2 ASO therapy for the purpose of monitoring drug toxicity, treatment efficacy and response. According to the Examiner, patients 2, 17 and 21 were administered a second course of treatment, where, for example patient 17 was retreated 48 hours after the initial course of therapy.

As noted above, claims 1 and 19 (and thus claims 3-5 and 7-18 and 20-23 dependent therefrom) are directed to a method of treating cancer in a human comprising, *inter alia*, administering a bcl-2 ASO in ***more than one cycle of therapy***, each cycle of therapy consisting of ***3 to 9 days***, wherein each cycle of therapy is ***separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered***. Thus, the claims are directed to what is known as "intermittent" therapy. To equate the discontinuance of therapy in patient 17 of Waters due to

toxicity with the intentional and desired intermittent therapy recited in the instant claims distorts the meaning of the term beyond all comprehension. In addition, as Dr. Novick notes in his Declaration, there is nothing to teach or suggest that patient 17's second course of therapy at lower dose was anything but the planned 14-day cycle required by the protocol. *See* Novick Decl., page 5, ¶ 19.

Furthermore, according to Dr. Novick, although patients 2 and 21 received a second course of treatment, there is no teaching or suggestion in Waters to shorten either of the courses of therapy from 14 days to 3 to 9 days, and thus is similar to Webb in this respect. *See id.*, page 5, ¶ 20. Also, there is no indication that any interval of time in which no bcl-2 ASO was administered separated the treatment courses, as required by the instant claims. *See id.*, page 4, ¶ 18. As such, it can hardly be said that Waters provides the motivation to one skilled in the art to administer bcl-2 ASO in an intermittent fashion to achieve clinical benefits, as alleged by the Examiner.

C. Bennett

Bennett discloses antisense compounds which modulate the expression of bcl-x. See col. 3, lines 61-65. Bennet is relied upon by the Examiner as disclosing the administration of bcl ASOs with one or more cancer agents that function by a non-antisense mechanism, such as 5-FU, etoposide and cisplatin. In particular, the Examiner states that Bennett teaches that "Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates [for bcl-x ASOs]." Thus, according to the Examiner, "One of ordinary skill in the art would have been motivated to vary the cycles or to vary the antisense dosage since it is routine and well known in the art to determine optimum dosages, dosing methodologies and repetition rates."

First, Appellants question the relevancy of Bennett to the instant claims. The instant claims are directed to ***bcl-2*** ASOs, while Bennett discloses the use of ***bcl-x*** ASOs. As even Bennett recognizes, these are distinct and independent apoptotic regulators. *See* col. 1, lines 32-44. Indeed, Example 31 in Bennett discloses that a bcl-x ASO did not affect the RNA expression of bcl-2. *See* col. 43, lines 19-24. The Examiner has provided no extrinsic evidence that determining the optimum dosages, dosing methodologies and repetition rates for bcl-x has any applicability to the administration of bcl-2. *See In re Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002) ("Thus when [Examiners] rely on what they assert to be general knowledge to negate patentability, that knowledge must be articulated and placed on the record. The failure to do so is not consistent with either effective administrative procedure or effective judicial review.").

In any event, Applicants submit that such boilerplate disclosure of ASO dosing as in Bennett does not suggest to one skilled in the art the claimed 3-9 day treatment period, even in view of Webb. In relying on so-called "routine practice," the Examiner has essentially made an *Aller* rejection, which stated that "where the general conditions of a claim are discovered in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

Subsequent cases, however, shed doubt on the reasoning in *Aller* in this type of rejection. For example, in *In re Yates*, 663 F.2d 1054 (CCPA 1981), the Examiner cited *Aller* for the proposition that "it is not inventive to discover optimum or workable ranges by routine experimentation." The court, in reversing the rejection, stated that "[t]he problem . . . with such 'rules of patentability' (and the ever-lengthening list of exceptions which they engender) is that they tend to becloud the ultimate legal issue – obviousness – and exalt the formal exercise of

squeezing new factual situations into preestablished pigeonholes. Additionally, the emphasis upon routine experimentation is contrary to the last sentence of section 103." *Id.* at 1056 n.4.

In *Yates*, the claim limitations at issue were the recitation of 25-80% conversion of olefin and a selectivity of less than 2% unsaturated acid. *Id.* at 1056. The applicant had provided examples from the prior art supporting the conclusion that the claimed results-effective variable, that is conversion, was simply not recognized as such by the prior art. *Id.* It was only under the conditions of the applicant's claims that a correlation between conversion and selectivity was discerned. *Id.* In the presence of such objective data, the PTO was directed to provide supporting references in order to refute such objective data. *Id.* at 1057. According to the Court, "mere allegations of obviousness are not enough." *Id.*

As with *Yates*, the Examiner in the instant case has exalted form over substance in rejecting the instant claims over Bennett. The Examiner's reliance on the superficial teaching of Bennett regarding optimizing dosing schedules amounts to a mere allegation of obviousness. Dr. Novick makes clear in his declaration that one skilled in the art would not have shortened the 14-day cycle in Webb, regardless of Bennett's boilerplate language regarding optimal dosing of ASOs. *See* Novick Decl., page 3, ¶ 14. Moreover, as noted above, Dr. Novick's declaration, in Tab A, provides examples of the prior art showing that the generally accepted course of bcl-2 ASO therapy was a 14-day treatment regimen. *See id.*, page 1, ¶ 3. Again, it was not until ***after*** Appellants' invention that others moved to shorter cycles of therapy. *See id.*, page 1, ¶ 4 and Tab B. In view of this evidence, and in the absence of any specific teachings to the contrary, reliance on the "routine practice" of dosing in Bennett amounts to nothing more than the "rule of patentability" discredited in *Yates*.

D. Combination of Webb, Waters and Bennett

Recognizing that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references," Appellants maintain that even if the references were combined in the fashion submitted by the Examiner, it still would not suggest to one skilled in the art the claimed invention with all its limitations. At most, one would obtain the generally accepted 14-day bcl-2 ASO treatment cycle (as taught by Webb) perhaps followed by a second generally accepted 14-day bcl-2 ASO treatment cycle (as taught by Waters), perhaps further comprising one or more cancer therapeutics (as taught by Bennett). However, as noted above, Dr. Novick makes clear in his declaration that one skilled in the art would not have shortened the 14-day cycle in Webb, regardless of reduced bcl-2 levels in Webb or Bennett's boilerplate language regarding optimal dosing of ASOs. Rather, the skilled artisan would have continued with longer courses of therapy given the overall unsatisfactory results provided in Webb and Waters. Again, this is consistent with the examples of the prior art provided in Tab A to Dr. Novick's declaration showing that the generally accepted course of bcl-2 ASO therapy was a 14-day treatment regimen. Immediately following Appellants' invention, the art quickly moved to shorter cycles of bcl-2 ASO therapy.

The Examiner's reliance on inherency belies the lack of suggestion in the art to shorten the generally accepted 14-day bcl-2 ASO treatment cycle. However, as discussed above, inherency has no place in this case. Reliance on inherency merely begs the ultimate question of nonobviousness, namely whether Applicants' claimed treatment regimen would have been obvious as a whole, by improperly shifting the burden to Appellants to somehow demonstrate that the 14-day treatment cycle of Webb did not have the additional ***unknown*** benefit of treating cancer at day 7. *See In re Mattsson*, Appeal No. 1996-1009 for U.S. Pat. Appln. 07/949,551

(BPAI 2000) (unpublished decision) ("Insofar as the examiner appears to making an *In re Best* type of analysis, we answer this question in the negative. While the heparin derivatives of the prior art do show a sulfur content, i.e., degree of sulfation, equal to or higher than the starting heparin from which they were derived, they have molecular weights ***lower*** than that of the starting heparin. . . . Thus, the examiner has not met her burden of establishing that the heparin derivatives of the prior art are identical or substantially identical to those of the claimed invention and, therefore, the burden has not switched to appellants to prove that the prior art heparin derivatives do not necessarily or inherently possess the characteristics of the heparin derivatives of the claimed invention.") (emphasis is original). Regardless of the improper burden shifting, the issue of inherency is irrelevant here, since "that which may be inherent is not necessarily known. Obviousness cannot be predicated on what is ***unknown***." *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (emphasis added); *see also In re Naylor*, 369 F.2d 765, 768 (CCPA (1966) ("[Inherency] is quite immaterial if, as the record establishes here, one of ordinary skill in the art would not appreciate or recognize that inherent result."); *Mattsson*, *supra* ("Furthermore, it is well established that inherency and obviousness are different concepts.").

Here, it is Appellants, and Appellants alone, who recognized the supposed "inherent" result that intermittent administration of bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily for 3-9 days was an efficacious treatment for cancer. The Examiner, notwithstanding her hindsight reconstruction, has pointed to nothing in the prior art to change this conclusion. A finding of obviousness based on these facts would mean, as noted above, that no novel shortened dosage regimen would ever be patentable, which surely is not the case. *See In re Shetty*, 566 F.2d 81, 86 (CCPA 1977) ("The Patent Office has failed to show a reasonable expectation, or some predictability, that Brake's compound would be an effective appetite

suppressant if administered in the dosage disclosed by Narayanan. The mere hindsight assertion that corresponding dosages render appellant's method obvious is untenable. Prior to appellant's disclosure, none of the adamantane compounds in any of the references before us suggested a use, much less a dosage, for curbing appetite."); *Adams*, 356 F.2d at 1001 ("The Patent Office presents a number of hindsight arguments. It says Adams was not the first to use foam for heat transfer as fire departments and fire extinguisher users have been squirting foam on fires for years and housewives have been pouring aerated water on cold plates in the kitchen sink for years, in both of which operations heat transfer is inherent. Of course it is inherent, otherwise appellant's invention would not work. But patentability here does not hinge on inherency. It depends on the unexpected and unsuggested increase in heat transfer efficiency. No reference suggesting this has been produced, only *ex post facto* explanations as to why anyone should have been able to see that it would be more efficient to use aerated water.").

In the end, whether based on motivation or inherency, the Examiner's rejection appears to rest on nothing more than the assertion that it is always obvious to modify a therapeutic dosing regimen to achieve optimal results, even in the face of teachings to the contrary. However, "obvious to try" is not the standard, as noted in *In re Antonie*:

> The PTO and the minority appear to argue that it would always be obvious for one of ordinary skill in the art to try varying every parameter of a system in order to optimize the effectiveness of the system even if there is no evidence in the record that the prior art recognized that particular parameter affected the result. As we have said many times, obvious to try is not the standard of 35 USC 103. *In re Tomlinson*, 53 CCPA 1421, 363 F.2d 928, 150 USPQ 623 (1966). Disregard for the unobviousness of the results of "obvious to try" experiments disregards the "invention as a whole" concept of § 103, *In re Dien*, 54 CCPA 1027, 371 F.2d 886, 152 USPQ 550 (1967) and *In re Wiggins*, 55 CCPA 1356, 397 F.2d 356, 158 USPQ 199 (1968), and overemphasis on the routine nature of the data gathering required to arrive at appellant's discovery, after its existence became expected, overlooks the last

> sentence of § 103. *In re Saether*, 492 F.2d 849, 181 USPQ 36 (CCPA 1974).

559 F.2d 618, 620 (CCPA 1977).

As in *Antonie*, the Examiner appears to have overemphasized the so-called "routine" nature of the clinical data gathering necessary to establish and support the claimed method of treatment, particularly after its acceptance by others in the art, and has failed to give proper weight to the nonobviousness of the invention "as a whole" under § 103. When viewed under the proper test, Applicants maintain that the Examiner has failed to make out a *prima facie* case of obviousness of claims 1, 3-5 and 7-23.

Applicants also submit that claim 5, directed to the method of treating cancer in a human of claim 1 or 3 comprising administering 5 to 7 mg/kg/day of the bcl-2 ASO, is nonobvious over the art of record for the ***additional reason*** that Waters, which enlarged the study of Webb, clearly states that the maximum tolerated dose of bcl-2 ASO was 4.1 mg/kg/day. *See* page 1815. As such, one of skill of the art would have been discouraged from increasing the dosage to the amount recited in claim 5 for the clinical treatment of cancer.

CONCLUSION

For the foregoing reasons, Appellants submit that claims 1, 3-5 and 7-23 are not unpatentable over Webb in view of Waters and Bennett, and reversal of the Examiner's rejections is therefore appropriate and respectfully solicited.

Respectfully submitted,

Date: September 22, 2008

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CLAIMS APPENDIX

1. A method of treating cancer in a human comprising administering to said human, in which such treatment is desired, a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day in more than one cycle of therapy, each cycle of therapy consisting of 3 to 9 days, wherein each cycle of therapy is separated by an interval of time wherein said human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day, and further comprising administering one or more cancer therapeutics.

3. The method of Claim 1, wherein each cycle of therapy consists of 4 to 7 days.

4. The method as in any of Claims 1 or 3 comprising administering 4 to 9 mg/kg/day of the bcl-2 antisense oligonucleotide.

5. The method as in any of Claims 1 or 3 comprising administering 5 to 7 mg/kg/day of the bcl-2 antisense oligonucleotide.

7. The method of Claim 1 wherein administration of the cancer therapeutic follows administration of the bcl-2 antisense oligonucleotide.

8. The method of Claim 1 wherein administration of the cancer therapeutic precedes administration of the bcl-2 antisense oligonucleotide.

9. The method of Claim 1 wherein the cancer therapeutic is administered concurrently with the bcl-2 antisense oligonucleotide.

10. The method of Claim 1 wherein said cancer therapeutic is a chemoagent, radiotherapeutic, immunotherapeutic, cancer vaccine, anti-angiogenic agent, cytokine, gene therapeutic, or hormonal agent.

11. The method of Claim 10, wherein said cancer therapeutic is a chemoagent, and wherein said chemoagent is dacarbazine, docetaxel, paclitaxel, cisplatin, 5-fluorouracil, doxorubicin, etoposide, cyclophosphamide, fludarabine, irinotecan or cytosine arabinoside (Ara-C).

12. The method as in any of Claims 1 or 10, wherein said cancer therapeutic is administered at a dose which is below the effective dose when the cancer therapeutic is administered without the bcl-2 antisense oligonucleotide.

13. The method as in any of Claims 1 or 3, wherein said administration is by oral, intravenous infusion, subcutaneous injection, intramuscular injection, topical, depo injection, implantation, time-release mode, intracavitary, intranasal, inhalation, intratumor, or intraocular administration.

14. The method as in any of Claims 1 or 3, wherein said cancer is a cancer of the hematopoietic system, skin, bone and soft tissue, reproductive system, genitourinary system, breast, endocrine system, brain, central nervous system, peripheral nervous system, kidney, lung, respiratory

system, thorax, gastrointestinal and alimentary canal, lymph nodes, pancreas, hepatobiliary system, or cancer of unknown primary site.

15. The method of any of Claims 1 or 3, wherein said cancer is non-Hodgkin's lymphoma, Hodgkin's lymphoma, leukemia, colon carcinoma, rectal carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, renal cell carcinoma, heptoma, bile duct carcinoma, choriocarcinoma, cervical cancer, testicular cancer, lung carcinoma, bladder carcinoma, melanoma, head and neck cancer or brain cancer.

16. The method as in any of Claims 1 or 3, wherein the antisense oligonucleotide is from 10 to 40 bases in length and is complementary to the pre-mRNA or mRNA ofthe bcl-2 gene.

17. The method of Claim 16, wherein the antisense oligonucleotide comprises at least two phosphorothioate linkages.

18. The method of Claim 17, wherein the antisense oligonucleotide comprises the sequence TCTCCCAGCGTGCGCCAT (SEQ ID NO: 17).

19. The method of treating cancer in a human comprising administering to said human, in which such treatment is desired, one or more chemoagents and a bcl-2 antisense oligonucleotide, wherein the bcl-2 antisense oligonucleotide is administered at a dose of 0.01 to 50 mg/kg/day in more than one cycle of therapy, each cycle consisting of 3 to 9 days, wherein each cycle of therapy is separated by an interval of time wherein said human receives no bcl-2 antisense

oligonucleotide, and wherein said interval of time comprises at least one day, and wherein the chemoagent is dacarbazine, docetaxel, paclitaxel, cisplatin, 5-fluorouracil, doxorubicin, etoposide, cyclophosphamide, fludarabine, irinotecan or cytosine arabinoside (Ara-C) administered at a dose which is below the effective dose when the chemoagent is administered without the bcl-2 oligonucleotide.

20. The method of Claim 19, wherein said chemoagent is paclitaxel and said dose is 10 to 135 mg/m^2/cycle.

21. The method of Claim 19, wherein said chemoagent is docetaxel and said dose is 6 to 60 mg/m^2/cycle.

22. The method of Claim 19, wherein said chemoagent is fludarabine and said dose is 2.5 to 25 mg/m^2/cycle.

23. The method of Claim 19, wherein said chemoagent is irinotecan and said dose is 5 to 50 mg/m^2/cycle.

EVIDENCE APPENDIX

Below is the Declaration of Dr. Steven Craig Novick Under 37 C.F.R. § 1.132, submitted on July 16, 2007.

Declaration of Dr. Steven Craig Novick

Qualifications of Dr. Novick

1. I, Dr. Steven Craig Novick, received a medical doctor degree from New York University School of Medicine in 1995. I received a doctorate degree in Molecular Oncology in 1994 from the same University. I have published numerous articles relating to various cancers and the use of certain therapies in the treatment of different cancers.

2. Since 2004, I have been serving as the Medical Director for Genta Incorporated. During this time I have assisted in the preparation of NDA filings for submission to the FDA to seek marketing approval for Genasense®. I assisted in the analysis and presentation of safety and efficacy data for Genasense. Genasense is a bcl-2 antisense oligonucleotide, also referred to as G3139.

Genasense Background and General Comments

3. Before the priority date of the '170 application (August 25, 2000), the generally accepted course of therapy was a 14-day treatment regimen. See chart attached at Tab A.

4. Not until after the present inventor's discovery that a shorter cycle of therapy would be useful in treating cancer, did others move to a shorter cycle of therapy. See chart at Tab B.

5. The first paper to discuss the use of a shorter treatment regimen (published after the filing date of the '170 application) was the Jansen et al. paper, Lancet, Vol. 356, pp. 17281733, (Nov. 18, 2000), which reports research sponsored by Genta. This paper shows efficacy in 14 patients where the patients received increased doses of BCL-2 antisense oligomer for a five-day cycle of therapy.

Summary of Conclusions: there is no teaching or suggestion in Webb and Waters to shorten the treatment regimen to less than a 2-week course of therapy

6. I have read and understood the subject application, U.S. 09/709,170 ("the '170 application").

7. I have also read the Office Action issued by the USPTO on November 28, 2006 and the two references referred to therein (Webb et al., The Lancet, 1997 Vol. 349; 1137-1141 ("Webb")) and Waters et al., Journal of Clinical Oncology, 2000 Vol. 18:1812-1823 ("Waters")).

8. I have concluded that one skilled in the art would not be motivated by the teachings of Webb and Waters to reduce the usual course of therapy for bcl-2 from a two week course of therapy to a three to nine day course of therapy, as presently claimed in the '170 patent.

9. The results reported in Webb and Waters are not impressive, and therefore, one skilled in the art reviewing these references would not be motivated to provide a shorter course of therapy, especially since most of all of the patients in the studies did not respond satisfactorily, despite 14 days of treatment. Those skilled in the art that develop drugs and treatment regimens do not routinely shorten cycles of therapy. To be motivated to do so (and to go against accepted treatment schedules) would require convincing results, which simply are not reported in Webb and Waters.

Webb Reference: no motivation to shorten the course of therapy

10. After reading the Webb reference, it is my opinion that this reference teaches a two-week treatment regimen. *See* Webb, p. 1137 left column: "A daily subcutaneous infusion of 18-base, fully phosphorothioated antisense oligonucleotide **was administered for 2 weeks** to nine patients. . . ." (emphasis added); *see also* page 1138, left column "**One 2-week course of treatment** was given. Patients were followed for 4 weeks after the end of treatment. If there was evidence of tumor response, a second course was considered." (emphasis added). Thus, in my opinion, one skilled in the art would read Webb as teaching a two-week course of therapy.

11. In my opinion, the mere fact that the authors in Webb report the bcl-2 levels of one patient (patient number 6) measured at week 1 and week 2 during the course of the two week course of treatment does not teach or suggest to one skilled in the art to treat a patient for cancer by shorting the regimen to less than the two week course of treatment, let alone shorten the course of treatment to a cycle of therapy consisting of three to nine days (as is presently claimed in the '170 application).

12. In my opinion, the mere fact that one patient (patient 6) at day 7 had reduced levels of BCL-2, does not provide evidence of treatment or a response, nor motivation to shorten the treatment regimen. One would not know whether the total infusion of 14 days was necessary to provide treatment of cancer or whether infusion of 7 days of therapy would be sufficient. This is especially the case, since the patient 6 did not show a promising cancer response.

13. One skilled in the art would understand that bcl-2 levels would in fact most likely go down with bcl-2 antisense treatment but would not know based on Webb's study whether this reduction represented a transient reduction or a stable reduction of bcl-2 levels. Further, one skilled in the art reading Webb would not know if this reduction of bcl-2 levels would likely treat cancer, especially if the bcl-2 reduction was transient.

14. In my opinion, one skilled in the art reading Webb would not be motivated to shorten the course of therapy, but rather would be motivated to continue with a longer course of therapy, or change the regimen to a course of therapy with a higher dose, or add to the regimen a second, third, or fourth (or more), course of therapy, or a combination of all of these changes to the regimen. In my opinion, by no means would one be motivated to shorten the course of therapy to treat cancer just because one patient showed reduced bcl-2 levels at week 1 and week 2, especially since patient 6 only showed a partial or negligible tumor response (page 2, column 1139).

15. Thus, it is my opinion that Webb does not teach or suggest changing the treatment regimen to anything shorter than a two-week course of therapy, let alone to a three to nine day course of therapy as presently claimed in the '170 application.

Waters reference: no motivation to shorten the course of therapy

16. After reviewing Waters, I conclude that this reference also teaches a course of therapy for two weeks. *See* Page 1812, first column: "Twenty-one patents with Bcl-2-positive relapsed NHL **received a 14-day subcutaneous infusion** of G3139. . ."(emphasis added); *see also* page 1813, left column: "Antisense oligonucleotide G3139 was delivered as a continuous subcutaneous infusion for **14 days** by a portable infusion pump. Toxicity was graded according to the common toxicity criteria and assessed **during the 2-week treatment period** and during the subsequent 4 weeks. One course of treatment was planned per patient, but additional courses of treatment were considered in the **event of a tumor response**." (emphasis added).

17. Because the purpose of this study was to determine safety ("These objectives provided the rationale for a phase I trial of antisense oligonucleotide G3139" page 1813, first col.), the authors studied and reported toxic events and noted that in certain patients, the treatment with bcl-2 antisense oligonucleotide was discontinued before completing the full 2-week course of therapy. See page 1815, col. 2. However, it is my opinion that stopping treatment during a course of therapy due to adverse events, does not teach or suggest using a shorter course of therapy to treat cancer.

18. Waters reports that certain patients had adverse effects and had their course of therapy terminated. For example, Patient 15's treatment was discontinued on day one, Patient 16's treatment was discontinued on day 12 and Patient 17's treatment was discontinued after day 2 (48 hours). *See* page 1815, col. 2. Thus, even if one skilled in the art would be motivated to shorten the cycle of therapy to treat cancer, there is nothing in this data to teach or suggest shortening the cycle of therapy to three to nine days, separated by an interval of time when the therapy is not given and repeating with another three to nine day cycle of therapy (as the current pending claim requires.)

19. Even if one were to read Waters as teaching Patient 17 only receiving 2 days of treatment followed by another course of therapy (since Waters reports that patient 17 received a second course of therapy), Waters still does not teach or suggest the claimed method of treating cancer where the patient is given a course of therapy of three to nine days, followed by a rest period, followed by another three to nine day course of therapy. First, patient 17 only received

two days of therapy as Waters states that treatment was discontinued after 48 hours because of dose limiting toxicity. Second, there is nothing to teach or suggest that Patient 17's second course of therapy at a lower dose was anything but the planned 14-day cycle required by the protocol. The discussion of Patient 17 therefore does not suggest the claimed invention, wherein multiple cycles of therapy each consist of three to nine days.

20. Waters reports that Patient 18's treatment was discontinued at day 8. However, there is nothing in article that states that Patient 18 went on to receive a second course of therapy. Waters mentions that only three patients (Patient 2, 17 and 21) received a second course of therapy. Waters but does not teach or suggest that it was Patient 18 and in fact clearly indicates by deduction that it was not Patient 18. *See* page 1813, first col. and page 1818, first col. Thus, there is no teaching or suggestion to shorten the course of therapy from 14 days to three to nine days and then continue on with another course of therapy of three to nine days after a rest period between.

21. In my opinion, even Waters was not impressed with the results of the study and therefore did not contemplate a shorter treatment regimen, but instead proposed a combination therapy. On page 1821, Waters notes that "[o]ne of the most interesting possibilities is their use as chemosensitizing agents . . . ." On page 1822, Waters further notes that "based on the results from this phase I study, a phase II trial is now in progress at Royal Marsden Hospital using G3139 in combination with standard cytotoxic regimens . . . " Thus, even Waters does not teach or suggest the use of a shorter treatment regimen, but rather suggest using BCL-2 in combination with cytotoxic reagents.

22. I, therefore, conclude that Waters does not teach or suggest a cycle of therapy to treat cancer consisting of three to nine days, followed by an interval of time where no bcl-2 antisense oligonucleotide is administered, followed by another three to nine day cycle of therapy (as required by the claims of the '170 application).

Conclusion

23. In addition to having no teaching or suggestion in Webb or Waters, it is my opinion, that one skilled in the art, reading Webb and Waters, would not have been motivated to treat cancer by shortening the cycle of therapy to from the accepted 2 week cycle of therapy to a cycle of therapy consisting of three to nine days, followed by an interval of time where no bcl-2 antisense oligonucleotide is administered, followed by another three to nine day cycle of therapy.

24. All statements made herein of my own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and may jeopardize the validity of the application or any patent issuing thereon.

4/26/07
Date

Dr. Steven Craig Novick

TAB A

Bcl-2 ANTISENSE PROTOCOLS BEFORE THE 09/709,170 APPLICATION PRIORITY DATE

April 26, 2000

AUTHOR	DATE	ROUTE	DAYS	COMMENTS
Webb	1997 ASCO (1997 Lancet)	SC infusion (daily w/ portable syringe driver)	14	bcl-2 protein levels measured at start of treatment, 2 weeks and 6 weeks. One patient was apparently assayed at 7 days as well (#5, Fig. 2), and had stable disease at week 3 (pg. 1139, tumor response). Patient 2 also had a decrease in bcl-2 protein and stable disease. 3 of 9 patients had stable disease or progressive disease on the study (little or no therapeutic benefit). A correlation between bcl-2 reduction and tumor response is not disclosed or suggested.
Morris	1998 ASCO	IV infusion	14	Patient bcl-2 levels not reported.
Waters	1998 ASCO	SC infusion	14	bcl-2 protein levels measured in tumor samples of 13 patients, and after treatment was reduced in 5 patients. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Jansen	1999 ASCO	IV infusion	14	Reduction in bcl-2 protein levels correlated with therapy. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Scher	2000 ASCO	Cont. infusion	14-21	At 4.1 mg/kg/d, bcl-2 protein expression decreased within one week, peak effect at 8-15 days. Conclusion: G3139 can decrease bcl-2 protein expression. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Chen	2000 ASCO	Cont. infusion	21	bcl-2 downregulation at doses ≥ 3 mg/kg/day. At 3 mg/kg/d, maximum bcl-2 reduction seen by day 3 of infusion. Tumor response observed in 2 patients. Contains no disclosure suggesting a correlation between bcl-2 reduction and tumor response.
Chi	2000 ASCO 2001 Clin Cancer Res	Cont. IV infusion	14	bcl-2 expression evaluated, no disclosure of results in abstract. Journal disclosure: bcl-2 protein reduced in 5 of 9 patients at 6 mg/kg/d at day 8. Patient 23 had >50% reduction in PSA, described as a good therapeutic response, but had only 10% reduction in bcl-2 levels (Fig. 1 and Fig. 2). Compare Patients 20 & 24 with 25-50% reduction in bcl-2 (Fig. 3), but who are not listed among those having a tumor response.

Bcl-2 ANTISENSE PROTOCOLS **BEFORE** THE 09/709,170 APPLICATION PRIORITY DATE
April 26, 2000

Waters	2000 J. Clin. Oncol. (May)	SC Infusion	14	See Tables 4 & 5. Patient 30% reduction in bcl-2 was less than half that of Patient 15 (15% vs. 39%) but both had stable disease. Patient 12 (32%) had a bcl-2 reduction comparable to Patient 19 (36%) but had progressive disease rather than stable disease. The largest bcl-2 reduction was Patient 6 (47%), who only had a minor response. Of the three patients who had bcl-2 assays at day 7, Patient 11 and Patient 12 had dramatically different therapeutic outcomes (stable disease vs. progressive disease) despite comparable reductions in bcl-2 expression (24% and 35% respectively). 9 of 21 patients had no change in bcl-2 levels in any tissue analyzed. Demonstrates there is no reliable correlation between reduction in bcl-2 expression and tumor response.

TAB B

BCL-2 ANTISENSE PROTOCOLS *AFTER* THE 09/709,170 APPLICATION PRIORITY DATE
April 26, 2006

AUTHOR	DATE	ROUTE	DAYS	COMMENTS
de Bono	2001 ASCO	Cont. IV infusion	5	Marked downregulation of bcl-2 by day 5. Contains no disclosure suggesting a correlation between downregulation of bcl-2 and tumor response.
Cotter	2001 ASCO	Cont. IV infusion	1-8	Marked downregulation of bcl-2 by day 6 at 5 mg/kg/d. Contains no disclosure suggesting a correlation between downregulation of bcl-2 and tumor response.
Janssen	2001 ASCO	Cont. IV infusion	5	bcl-2 downregulated by day 4. Contains no disclosure suggesting a correlation between downregulation of bcl-2 and tumor response.
Morris	2002 Clin. Cancer Res.	Cont. infusion	14 or 21	bcl-2 protein levels are shown for a single patient, and did not decline until day 15 of treatment. No major antitumor responses were observed - 37% had stable disease during treatment and 57% progressed (pg. 881, col. 2, "Clinical Effects"). "These studies are ongoing, as are determination of the association between clinical effects, dose and the timing and degree of bcl-2 protein reduction." (pg. 882, last sentence)
Rosen	2003 ASCO 2004 J Clin Oncol	Cont. IV infusion	1-8	No evident suppression of bcl-2 in peripheral blood mononuclear cells on day 6 of treatment (pg. 1114, Analysis of bcl-2 Suppression...). These data are consistent with prior clinical reports (pg. 1113, last column - see Waters , J Clin Onc 2000 and Morris - Clin Cancer Res 2002, above; Chi - Clin Cancer Res 2001 and Marcucci - Blood 2003, below).
Dennidow	2003 ASCO	Cont. IV infusion	7	Analysis of bcl-2 levels not disclosed.
Eskens	2004 ASCO	Cont. infusion	5	Analysis of bcl-2 levels not disclosed.
Marcucci	2004 Ann Oncol	Cont. infusion	21 5	Dose limiting toxicities prevented dose escalation beyond 4 mg/kg/day in 21 day infusion protocol. In 5 day infusion protocol even highest doses were tolerated without dose limiting toxicity. Shortened infusion had less cumulative toxicities and still allowed similar total delivery as the longer infusion.

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Tab B

BCL-2 ANTISENSE PROTOCOLS *AFTER* THE 09/7709,170 APPLICATION PRIORITY DATE
April 25, 2006

Latest Priority Date of Genta Patent Application - 10 November 2000 - (Dark Line)
ASCO Annual Meetings are held in late May/early June
Conclusions: Prolonged infusion was the standard protocol prior to Nov. 2000.
Following filing of the Genta patent application, the field quickly adopted the short infusion protocol of the invention because it allowed higher doses to be tolerated.
Treatment of cancer does not necessarily result from decreases in bcl-2 levels.
Therefore, observation of bcl-2 downregulation does not indicate cancer is inherently treated.

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Tab 3

RELATED PROCEEDINGS APPENDIX

None.